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(57) Abstract

A composition intended as a diet fortification to increase the efficiency at muscle work wherein the composition includes, beside any nutrients, salts, vitamins, trace substances, flavourings, aromatics, etc., known in themselves, ubiquinone (coenzyme Q_{10}) as the essential component.

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DIET FORTIFICATION

The present invention relates to a composition intended to constitute a diet fortification for the temporary and/or long-term improvement of the efficiency at muscle work of the individual who takes the diet fortification, and it relates moreover to the application of such a composition.

A great number of beverages are on the market which are intended to be taken in cases of prolonged physical exertion in order to replace above all the loss of fluid the body has suffered through perspiration. It is a further objective of these beverages to replace the glucose and the salts in blood and muscles which have been consumed and/or lost. The beverages, therefore, are aqueous solutions containing different carbohydrates. The beverages of the type mentioned here are often referred to as sports beverages.

The transformation of energy in the musculature depends not only on the supply of substrate for energy transfer but also depends on the metabolic preconditions required so that optimum breakdown in the muscle fibres can be achieved. This applies especially to hard and frequently prolonged physical exercize e.g. during training and competitive activity but also in cases of temporary physical strains in skilled work or in other stress situations with pronounced muscular activity (e.g. contractures).

It is the objective of the present invention to provide a composition intended primarily for healthy, physically active persons, where the composition is apt to improve the opportunities for training and thus obviously increase the physical exercize capacity. The composition is primarily intended for active persons which have reached a very high level of training, such as long-distance runners, boxers, cyclists, swimmers, decathletes and the like. Such a high level can readily be determined by those skilled in the art of sporting using inter alia ergometer-cycle techniques. Reference is made to literature available within this area (cf. PH Åstrand: Ergometri-Konditionsprov, 1962, Folksam Skriftserie). The composition

includes ingredients which can inactivate certain harmful by-products of the metabolism. The formation of such harmful substances, e.g. free oxygen radicals, are a normal biological phenomenon, and the cell has developed a number of protective mechanisms for this purpose. Examples of these are so-called antioxidants with "trapper"-, "quencher"- or "scavenger"-like properties; terms of English origin which figuratively describe the function.

Endurance work is characterized in that large quantities of oxygen (O_2) are transported to the musculature for the purpose of being used in the combustion metabolic process, carbon dioxide (CO_2) and water (H_2O) being formed. Such metabolic processes involve a gradual breakdown of fats and carbohydrates so as to release chemically bonded energy. A basic requirement for endurance work, therefore, is a good supply of oxygen in the muscle fibres. The term fitness also refers to the capacity available for taking up and transporting oxygen to the working musculature. This capacity in turn determines:

1. what level of working intensity can be maintained without appreciable quantitites of lactic acid being formed in the active musculature and accumulated there, which detrimentally affects the working capacity (physical fatigue), and

2. what level of "maximum" working intensity can be maintained (symptom-limited working capacity), which is determined by the combination: capacity for oxygen transport and lactic acid tolerance in the working musculature.

The critical value for lactic acid formation in point 1, that is to say the OBLA-value (Onset of Blood Lactate Accumulation), corresponds to a highest work load for an individual with regard to endurance work. The maximum working capacity according to point 2 or the SL-value (Symptom Limited) signifies the "ceiling" of efficiency and provides, inter alia, information as to the maximum lactic acid

concentration in muscle and blood. Ergometer cycle and graded work, that is to say stepwise increase of intensity (20-40 W) per minute are used in the so-called OBLA/SL-test. For the OBLA and SL values respectively thus obtained the symbols W_{OBLA} and W_{SL} are used, and the unit here is Watt (W).

It also has been found that the periphery, that is to say the working muscles, are of great importance for the energy transformation during prolonged hard work. Thus, it can be said that, in addition to increased oxygen uptake, individuals with great endurance are characterized by a high percentage of slow muscle fibres and high capillary density. In addition such individuals possess a high activity of the enzymes which participate in the combustion process. Corresponding activities concerning lactic acid formation on the other hand are lower. As a whole this means that the combustion capacity increases whilst the lactic acid formation, and thus the fatigue-inducing factors, diminish.

For the working muscles and their fibres certain substances (cofactors) are essential, and sometimes of decisive importance for optimum coupling and thereby function in the gradual breakdown. This brings about less risk of "energy leakage" and radical formation associated therewith. Cofactors have different functions in the muscle cell: they activate e.g. the enzymes which participate in the breakdown and transformation of chemically bonded energy to other forms of energy, e.g. mechanical work, via ATP and creatin phosphate. Other substances, which sometimes are summed up under the concept cofactors, also can be effective as "detoxication units" in the metabolism. The body is able to control the formation of oxygen radicals under normal conditions and the formation consequently can be handled and tolerated by the tissue in question. In cases of enhanced transformation of energy and/or metabolic stress induced by other causes, the formation of free radicals increases and there are grounds for assuming that the increase is positively accelerating with the heightened transformation of energy. When cofactors are

supplied the trained muscle, as part of the total local training effect, also has an increased capacity for handling radical formation. Shortage of cofactors in the trained musculature may lead to damages which occur first on intracellular level, frequently without any symptoms. In the damages are allowed to escalate, however, more general tissue damages ("inflammatory processes") occur, which often are associated with local irritation-pain conditions and similar symptoms which may even become disabling.

Generally, it can be said that the effect described above, of capturing and rendering harmless radicals, and especially oxygen radicals, is of fundamental importance for enhancing, temporarily as well as long-term, the efficiency of the muscles and thereby of the individual. It is particularly important that the functions which are induced by training are utilized in an optimum manner.

The present invention relates to a composition containing substances (cofactors) which contribute to a more effective transformation of energy and "detoxication" in connection with the metabolism.

The present invention especially relates to a composition primarily intended to be consumed by individuals which have reached a very high level of training, and as a further aspect the invention relates to a method of use of the composition comprising administering an effective amount of the composition for increasing the capacity at muscle work and especially the capacity of such well trained individuals.

It has been found surprisingly that by taking the composition it is possible to achieve a substantial reduction of the aforementioned problems and to achieve, moreover, an improved efficiency in connection with training/competition. The composition is intended in the first place to be used in conjunction with the supply of energy through the intake of food and/or drink. In certain applications the composition is added, therefore, to the food and/or drink which is to be taken.

The composition includes as the essential component the coenzyme Q_{10} (hereinafter called CoQ_{10}) chemically known as ubiquinone. According to what has been found so far, CoQ_{10} has several functions:

1. In the mitochondria (combustion units of the muscle cell) it holds together the functions between the citric acid cycle and the respiratory chain (the reaction of oxygen and hydrogen ions in a redox system to form water). CoQ_{10} brings about not only a biochemical but also a purely physical coupling inside the mitochondria between these different functions and functional units. This causes CoQ_{10} to be very active in case of an excess of electrons.

2. In its reduced form (quinol form) it acts in the mitochondria structure as anantioxidant. Differently from e.g. glutathione, however, it does not enter into a "recycling system" but is broken down in the microsomes of the cell and in the liver and is extracted.

3. In the space between the cell wall and the mitochondria it facilitates the electron transport, so far as can be judged in connection with lactic acid formation. There are many indications that CoQ_{10} in this environment too has a "trapper"- and "scavenger"-function, analogously to that in the mitochondria.

Beside CoQ_{10}, the composition as a rule includes nutrients, salts, vitamins, trace substances, flavourings, aromatics etc, known per se.

To enhance further the readiness and capacity of the muscles to handle prolonged and heavy exercize L-carnitine and/or pyridoxine (vitamin B_6) are incorporated into the composition in accordance with an embodiment of the invention. In certain applications salts and/or derivatives of L-carnitine and/or pyridoxine are included in the composition. Carnitine has a key function in the transport of free fatty acids into the mitochondria and in the combustion of fatty acids to carbon dioxide and water. If carnitine, and hence the

conveyor of free fatty acids is lacking, these will accumulate intracellularly in even higher concentrations. Free fatty acids have a releasing effect on the mitochondria breathing with a consequent increased radical formation. Although the role of B_6 has not been clearly established, there is evidence that its presence has a positive effect on the CoQ_{10}-level. In addition it is a fact that on shortage of B_6 the glycogen metabolism is altered.

In accordance with another embodiment of the invention α-ketoglutaric acid, salts and/or derivatives thereof are included in the composition. It has been found in tests carried out by the applicant that on taking α-ketoglutaric acid, salts and/or derivatives thereof, especially in combination with pyridoxine, salts of pyridoxine and/or derivatives thereof, the lactic acid concentration during hard physical labour is reduced and a positive effect on the metabolism of carbohydrates also occurs. Quite generally the tests have shown that a protective effect against free radicals is also produced. When the quantities of α-ketoglutaric acid, salts and/or derivatives thereof related B_6 are within the range 1:10 - 10:1 and in particular in the range 1:5 - 5:1 the effect is especially favorable. The absorption of the aforementioned substances in the intestine is individually conditioned, but for reaching the intended effect e.g. the following daily doses taken orally have proved appropriate:

CoQ_{10}	10- 700 mg	preferably	10-500 mg
L-carnitine	100-5000 mg	"	200-3000 mg
pyridoxine	10- 800 mg	"	20- 500 mg

Corresponding effects are achieved if the daily dose is taken in the form of salts or derivatives of the substances.

In order to facilitate the absorption in the intestine it is preferable if the components are available in water-soluble, dispersable and/or water-miscible form.

The upper limit values given have been found to lie well below the levels which in healthy, voluntary test subjects can produce side effects in any form.

In accordance with a further preferred embodiment complementary substances are included which participate in the rendering harmless of radicals. Examples of these are selenium, tocopherol (vitamin E), glutathione etc.

The composition of the invention can be produced by conventional blending techniques well known to those skilled in the art and requiring no further elaboration herein. In the event that hygroscopicity should prove to involve any difficulty in the blending, it is sufficient to effect the blending under anhydrous conditions as also well known to those skilled in the art .

Test 1 - Description of indication

A great number of healthy, middle-aged men with varying physical exercize capacity/training volume have been examined so as to determine the normal value of CoQ_{10} in the blood and skeletal muscles (external thigh muscle, m. vastus lateralis). The mean value of CoQ_{10} in the skeletal muscle was 0.18 mg x g^{-1} with a variation corresponding to 0.07-036 mg per gram. The corresponding value for venous blood was 0.7 mg x ml^{-1}. The muscle as well as the blood data for CoQ_{10} indicate that great individual variations exist for individuals who otherwise are clinically in good health. The lowest values in muscle and blood exist in the concentration region which is regarded as pathological in conjunction with illnesses such as cardiomyopathy or cardiotoxicity induced by medicines such as e.g. Adriamycin^{R}.

It was possible to show that the variation in the CoQ_{10} content in the skeletal muscle varies jointly with the quality of the muscle expressed as the percentage of slow (LF) muscle fibres ($r = 0.62$, $p < 0.001$). There was also a positive connection if the CoQ_{10} content of the muscle was related to the physical exercize capacity expressed as e.g. W_{OBLA} related to the body weight ($W \times kg^{-1}$) ($r = 0.70$, $p < 0.001$). Individuals with a high physical exercize capacity (varies jointly with a high percentage of LF in the muscles) in accordance with the experiment thus have a clearly higher CoQ_{10} content in the muscles than individuals with a lower physical exercize capacity. It is also well established that the training volume varies jointly with the physical exercize capacity .

The most important source for incorporating CoQ_{10} into the skeletal muscles is the CoQ_{10} in the blood circulation. The concentration of CoQ_{10} in the blood amounts to approx. 350-400 % of that in the skeletal muscles. However, the CoQ_{10} content of the blood was found to be negatively related to the physical exercize capacity irrespectively of whether it is expressed as W_{OBLA} or W_{SL} in relation to the body weight ($r = -0.48$, $p < 0.001$, and $r = -0.43$, $p < 0.01$). This means that individuals with high physical working capacity/training volume and with high values of CoQ_{10} storage in the skeletal muscles had clearly lower blood values than individuals who were physically inactive. This relation must be taken as an expression indicating increased storage of CoQ_{10} with increased working capacity/training, increased "turn-over" depending on the increased metabolism and a certain limitation with regard to the supply of CoQ_{10} in order to maintain corresponding blood values at "normal" level.

The storage of CoQ_{10} in the skeletal muscles is conditioned by the higher capacity for energy transformation, above all for combustion in the slow fibres of the skeletal muscles and their mitochondria. This has been studied earlier clinically in various patient categories, e.g. cancer patients which show signs of cardiotoxicity owing to Adriamycin^{R}-treatment, patients with cardiomiopathies and patients with strain angina. In all these cases low, and sometimes

extremely low. CoQ_{10} values in the muscles coincide with far-reaching histopathological findings with inter alia rupturing of the mitochondria. The most immediate comparison with healthy test subjects can be made in respect of patients with strain angina and where mitochondria rupturings exist above all in the slow fibres and this leads inter alia to a strong impowerishment of the combustion capacity of the slow fibres.

To understand fully the storage of CoQ_{10} by the skeletal muscles in healthy test subjects the values for CoQ_{10} have to be related to the actual combustion capacity of the skeletal muscles either expressed as the percentage of slow fibres or as a marker for the mitochondria function, e.g. the activity in respect of citrate synthesis (CS). Whatever comparison is made, it shows that otherwise healthy test subjects with a high percentage of slow fibres show a similarly low relative storage of CoQ_{10} in the skeletal muscles as the group of patients with strain angina referred to above. Consequently there are grounds from a relative point of view to classify the CoQ_{10} content of the skeletal muscles of individuals with high physical exercize capacity/training volume as low compared with individuals with a lower degree of physical activity.

Summing up it can be said, therefore, that the CoQ_{10} values of the skeletal muscles increase with the exercize capacity/training volume whilst an inverse relationship exists for corresponding blood values which under certain conditions (metabolic stress situations) gives rise to deficiency situations regarding the provision of the muscles with precursors for the mitochondria function. If the CoQ_{10}-content of the skeletal muscles was related to the simultaneous respiratory capacity or mitochondria function, the experimental results obtained also indicate that individuals with a high working capacity/training volume have lower values than individuals with a lower degree of physical activity. According to the test results otherwise healthy individuals with high working capacity/training volume run the risk of finding themselves in situations corresponding to a shortage of

CoQ_{10} for storage in the skeletal muscles and thus increased risk of escalating radical formation with accompanying cell damages and impaired function, a situation which is not too uncommon among the sporting elite.

Test 2 - Treatment of healthy, largely inactive men and women

In order to evaluate the tolerance, changes in working capacity and in the CoQ_{10}-count of the blood tests were carried out with four groups (1-4) of test subjects which were treated with placebo (group 1), carnitine (group 2), diet fortification version 1 (group 3), hereinafter designated TLI (see Table below), or CoQ_{10} on its own in sesame oil formulation (group 4). The L-carnitine treatment amounted to 1000 mg per day and the CoQ_{10} treatment to 100 mg per day.

Table 1

TLI:	Na2-α-ketoglutarate	1050
	L-carnitine	1000
	Pyridoxine	20
	CoQ_{10}	100

All quantities are given in mg

After a preliminary test (control test) the test subjects were reexamined after 4 and 8 weeks treatment. Slight digressions were recorded, but these were completely randomized and were due to factors other than side-effects.

The different treatment regimes were tolarated well (no side-effects were noted) and did not in any way detrimentally affect the test subjects. The CoQ_{10} concentration in the venous blood was determined in the control test and after 4 weeks of treatment. The

basic values which were measured in the control test were wholly comparable between the four groups. After 4 weeks of treatment the concentration had increased for groups 3 and 4, that is to say those which were treated with CoQ_{10} (in mixture - TLI - or on its own). The test results are evident from Figure 1 which shows the CoQ_{10} content of the four test groups in the control test and on re-examinations after 4 weeks of treatment. The increase of the CoQ_{10} of group 3 and 4 was 90 and 175, respectively. The absolute values in the majority were below what is regarded as the clinically therapeutically effective region (2-3 $\mu g \times ml^{-1}$).

The W_{OBLA} was not affected by anyone of the treatment regimes. It could be shown, though, that the intake of CoQ_{10} did alter the W_{SL}, that is to say the maximum working capacity. With regard to W_{SL} it is a fact that it depends on the capacity of the muscle to carry out aerobic work as well as on the anaerobic development of energy, that is to say lactic acid formation and release of lactic acid to the extracellular space and, inter alia, the blood circulation. Experimental results showed that after 8 weeks of treatment the interrelationship between W_{SL} and the highest lactic acid concentration in the blood measured had changed for group 3 and 4. The interrelationship is shown graphically in Fig. 2a and 2b for the two groups 3 and 4 together. Fig. 2a relating to the result before the treatment with CoQ_{10} (on its own) or with TLI and Fig. 2b after the treatment with CoQ_{10} and TLI (same daily dose CoQ_{10}). The lactic acid concentration in the blood, BHLA, is indicated in the Figures along the X-axis ($nmol \times 1^{-1}$) and W_{SL} along the Y-axis (W). It is evident from the result that after 8 weeks of treatment the interrelationship between W_{SL} and BHLA, $W_{SL}=f(BHLA)$, had a steeper slope than in the control test and that the highest values of W_{SL} were attained at higher values of BHLA than in the control test. It is clear from the result that the test subjects after treatment during 8 weeks tolerated higher values of BHLA which in turn resulted in higher values for W_{SL} than before the treatment. Corresponding changed did not exist in groups 1 and 2 after treatment during 4 and 8 weeks, respectively.

Test 3 - Treatment of healthy and physically active men

In order to evaluate the connection between diet additives and hard systematic training, physically active test subjects were studied. They are sportsmen with regular running training each week (up to the order of magnitude of 10-12 miles for long-distance runners forming parts of a group). The test subjects were divided into two groups and treated blindly (placebo and active treatment with TLII whose content is given below in Table 2).

Table 2

TLII:	Na_2-α-ketoglutarate	1050
	L-carnitine	1000
	Pyridoxine (B_6)	500
	CoQ_{10}	100

All quantities are given in mg

Fig. 3 illustrates the physical exercize capacity measured before and after treatment with TLII expressed as W_{OBLA} and W_{OBLA} per kg body weight respectively in panels A and C. The panels B and D indicate corrsponding values expressed in per cent of base level, that is to say in per cent of the values at time 0 (control test).

It is evident from the test results that the physical exercize capacity expressed as W_{OBLA} measured was higher for both groups after 4 weeks as well as after 8 weeks of treatment, 9 % and 12 % respectively (Fig. 3A and B), but the change was significant only for the group which had been treated with TLII. The picture remained the same if the W_{OBLA} values were related to the individual body weights. The improvement then was 8 % (4 weeks) and 12 % (8 weeks) respectively for the test group which was under active treatment. Fig. 4a and b refer to the symptom-limited working capacity, W_{SL}. Fig. 4a indicates the absolute values at weeks 0.4 and 8 and Fig. 4b shows

the changes after 4 and 8 weeks respectively in per cent of the values in the control test (week 0), W_{SLO}.

Regarding the symptom-limited work load ("maximum work"), the measured values showed and increase in the working capacity for the group which was under TLII treatment, amounting to 8 % after 8 weeks compared to 3 % for the placebo group (lefthand blocks in Fig. 4b).

SUMMARY AND CONCLUSIONS

In general it can be stated that a normally functioning muscle metabolism presupposes beside the normal enzymatic machinery also a capacity for taking charge of the radical formation which always occurs in connection with the metabolism of substances. The free radicals, especially the oxygen radical, would otherwise have a detrimental effect on subcellular and cellular structures which may lead to damages and inflammatory processes in the end, with an irritation/pain as part of the symptom picture. The normal muscle fibres have a number of biological systems to render harmless the radicals formed and the term antioxidants is used parallel with the English terms "trapper"-, "scavenger"- and "quencher"-function.

The antioxidant activity depends on substances being supplied to the musculature which in many connections are summed up under the designation cofactors and in a more popular connection "vitamins". Many of these possess a direct activity to take charge of radicals formed whilst others reduce the possibilities of radical formation above all in case of enhanced metabolism which is the case during hard physical exercize such as training and competition. Most of these substances are supplied to the body via the nourishment and, on condition that they are qualitatively acceptable, there are grounds for assuming that no deficiency situation ought to arise. However, under training and competitive conditions (mainly on elite level) there is an obvious risk of shortage in intake and hence in the normal antioxidant function of the muscles and consequent muscular damage.

An important antioxidant function of this kind is performed by the coenzyme Q or CoQ_{10} especially in its reduced form. Normally CoQ_{10} takes part in the electron transport between the citric acid and the respiratory chain but the reduced form is also very active when it comes to rendering harmless especially free oxygen radicals. The tests described above have shown that healthy male test subjects with varying degrees of activity have a strongly individual variation in the CoQ_{10} content of the muscle as well as of the blood. Tests have shown that in the muscles the CoQ_{10} content increases positively with increased physical working capacity or percentage slow muscle fibres whilst the content in respects of the blood circulation is negatively related to the working capacity. If the content in the skeletal muscles is standardized in relation either to the muscle fibre composition or to a marker of the mitochondria function, values are obtained which suggest possibilities of a biological deficiency situation in the skeletal muscles, above all in physically extremely active individuals. This applies primarily to intensively competing and severely trained individuals with high physical exercize capacity expressed as fitness, that is to say the capacity of hard exercize during prolonged periods and consequently high oxygen metabolism in the skeletal muscles.

Different treatment regimes have been tested on voluntary test subjects; either physically largely inactive or trained individuals. Physically inactive individuals are affected only by CoQ_{10} as such or in combination with other substances (say TLI) in that the symptom-limited working capacity (W_{SL}, "maximum" working capacity) was altered to such a degree that W_{SL} before the treatment was not related to the maximum lactic acid concentration in the blood, but that such a positive connection existed after treatment. Those who increased their lactic acid concentration in the blood also increased their maximum working capacity. No alteration of the submaximal working capacity e.g. W_{OBLA} was observed in the physically inactive test subjects.

Physically active individuals which are treated with a cofactor regime (say TLII) increased their working capacity as a result of the treatment. In tests on an ergometer cycle an increase of the submaximal working intensity, W_{OBLA} was found and the effect of the treatment, moreover, was particularly pronounced in respect of the symptom-limited working capacity, W_{SL}.

The voluntary test subjects reported no serious side effects from the respective treatment and the negative experiences which were reported were wholly randomized and relatively speaking wholly negligible.

CLAIMS

1. A composition intended for oral intake to be used as a diet fortification to increase the efficiency at muscle work, c h a r a c t e r i z e d in that the composition includes as the essential component ubiquinone (coenzyme Q_{10}) possibly together with substances known per se such as nutrients, salts, vitamins, trace substances, flavorings, aromatic, etc.

2. A composition in accordance with claim 1, c h a r a c t e r i z e d in that the composition also includes L-carnitine, salts of L-carnitine and/or derivatives of L-carnitine.

3. A composition in accordance with claim 1 or 2, c h a r a c t e r i z e d in that the composition includes pyridoxine (B_6), salts of pyridoxine and/or derivatives of pyridoxine.

4. A composition in accordance with anyone of claims 1-3, c h a r a c t e r i z e d in that the composition includes α-ketoglutaric acid, salts and/or derivatives thereof.

5. A composition in accordance with claim 4, c h a r a c t e r i z e d in that the α-ketoglutaric acid, salts and/or derivatives thereof are included in the composition related to vitamin B_6 in a weight ratio of 1:10-10:1, preferably in a ratio of 1:5-5:1.

6. A composition in accordance with one or more of the preceding claims, c h a r a c t e r i z e d in that at least the ubiquinone present in the composition is in a water-soluble, water-dispersable and/or water-miscible form.

7. A composition in accordance with one or more of claims 2-6, c h a r a c t e r i z e d in that the composition contains ubiquinone, salts and/or derivatives thereof in a quantity of 10-700 mg, preferably 10-500 mg, the quantity specified relating to daily intake.

8. A composition in accordance with anyone of claims 2-7, c h a r a c t e r i z e d in that the composition includes L-carnitine and pyridoxine, salts and/or derivatives thereof in the quantities 0.1-5 g and 20-800 mg respectively, preferably 0.2-3 g and 20-500 mg respectively, the quantities specified relating to daily intake.

9. A composition in accordance with one or more of the preceding claims, c h a r a c t e r i z e d in that the composition includes further substances which render harmless free radicals e.g. selenium, tocopherol (vitamin E), glutathione, vitamin A etc.

10. Use of ubiquinone (coenzyme Q_{10}) as the essential component in diet fortification to increase the efficiency at muscle work.

11. Use in accordance with claim 10, c h a r a c t e r i z e d in that ubiquinone is present together with L-carnitine, salts and/or derivatives of L-carnitine, pyridoxine (vitamin B_6) and/or salts and/or derivatives of pyridoxine.

12. Use in accordance with claim 10, c h a r a c t e r i z e d in that ubiquinone, L-carnitine and pyridoxine, salts and/or derivatives thereof are included in quantities of 10-700 mg, 0.1-5 g and 20-500 mg respectively, preferably 10-500 mg, 0.2-3 g and 20-500 mg respectively calculated on daily intake.

13. Use in accordance with anyone of claims 10-12, c h a r a c t e r i z e d in that α-ketoglutaric acid, salts and/or derivatives thereof are included related to B_6 in a weight ratio of 1:10-10:1, preferably in a weight ratio of 1:5-5:1.

14. Use in accordance with one or more of claims 10-13, c h a r a c t e r i z e d in that substances which bond free radicals e.g. selenium, tocopherol (vitamin E), glutathione, vitamin A etc. are included.

15. A method of use of the composition claimed in claims 1-9 comprising administering an effective amount thereof to an individual for increasing the capacity at muscle work.

16. A method as claimed in claim 15, comprising administering said composition to an individual having reached a very high level of training for increasing the capacity of said individual.

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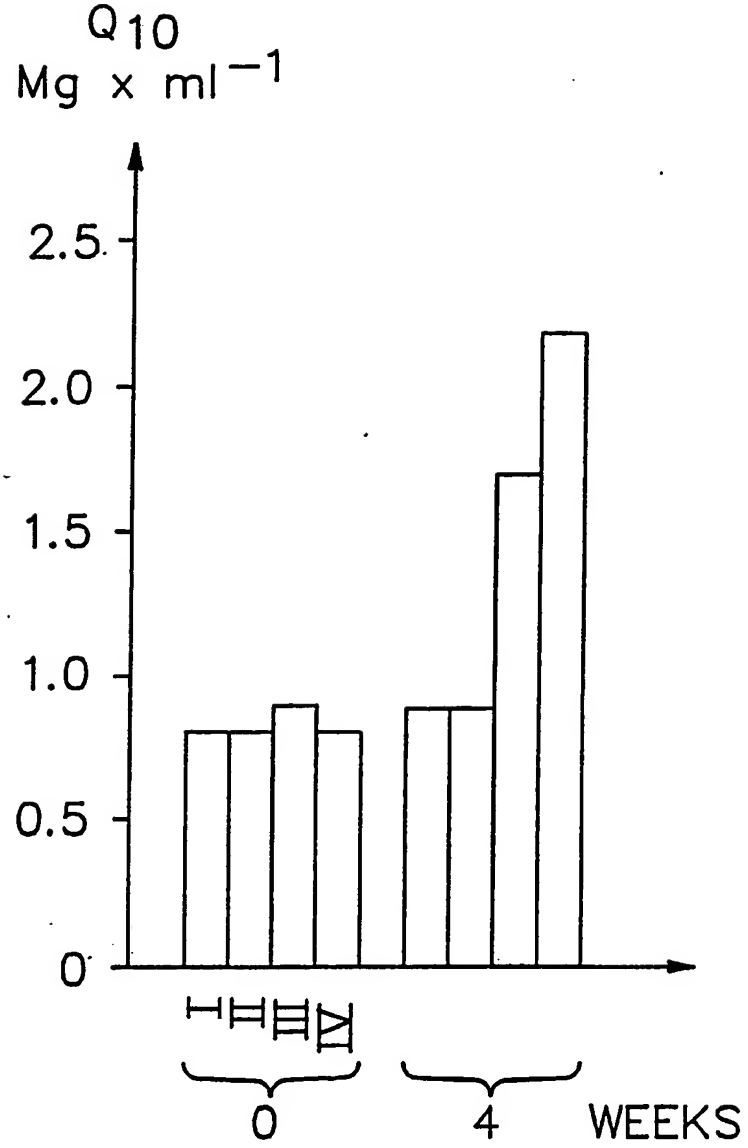

Fig. 1

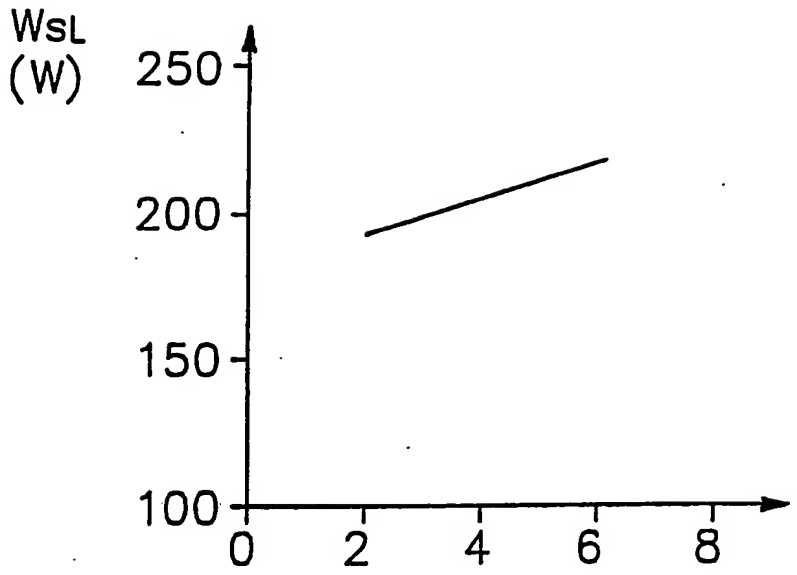
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Fig. 2a

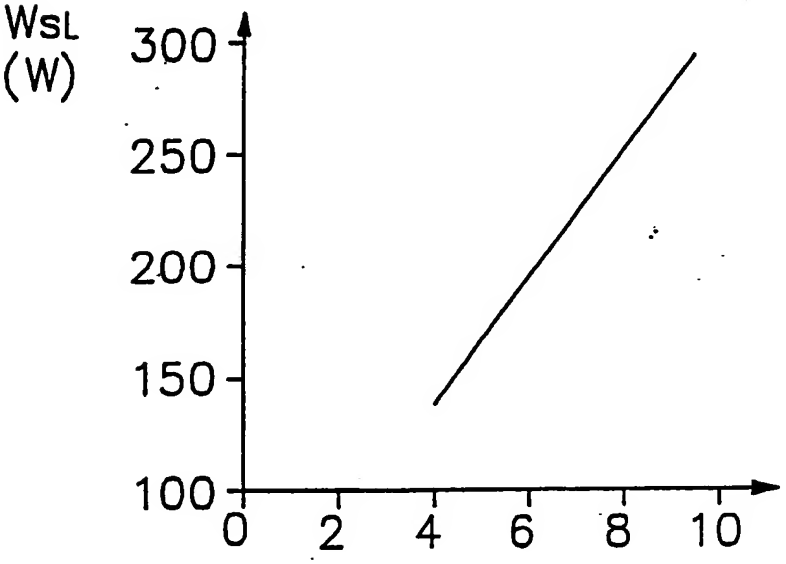

WsL
(W)
300
250
200
150
100
0
2
4
6
8
10
BHLa
mmoo1 x 1

Fig. 2b

Fig. 3a

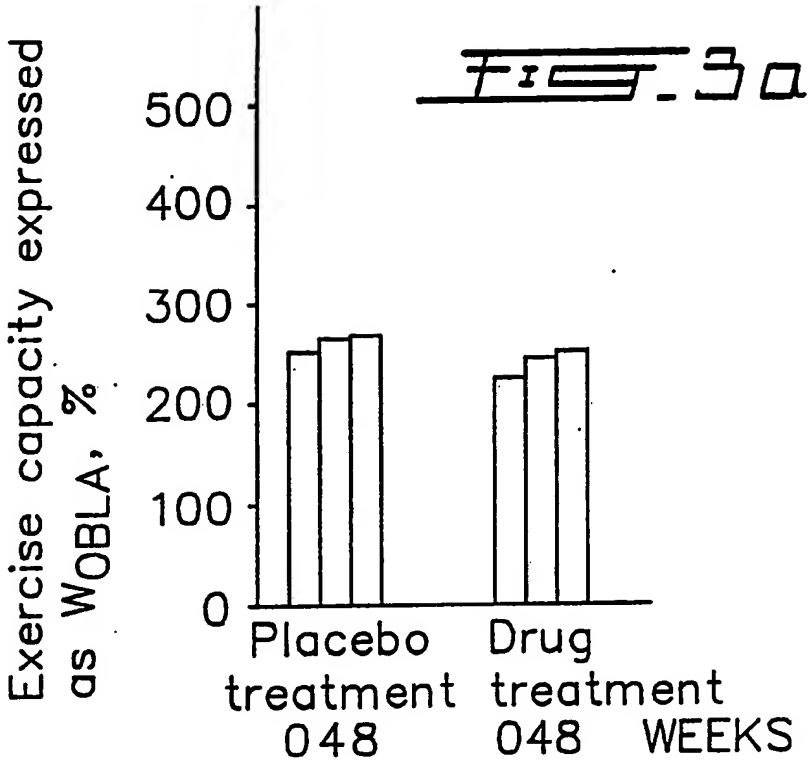

Exercise capacity expressed as W_{OBLA}, %
500
400
300
200
100
0
Placebo treatment
Drug treatment
0 4 8
0 4 8 WEEKS

Fig. 3b

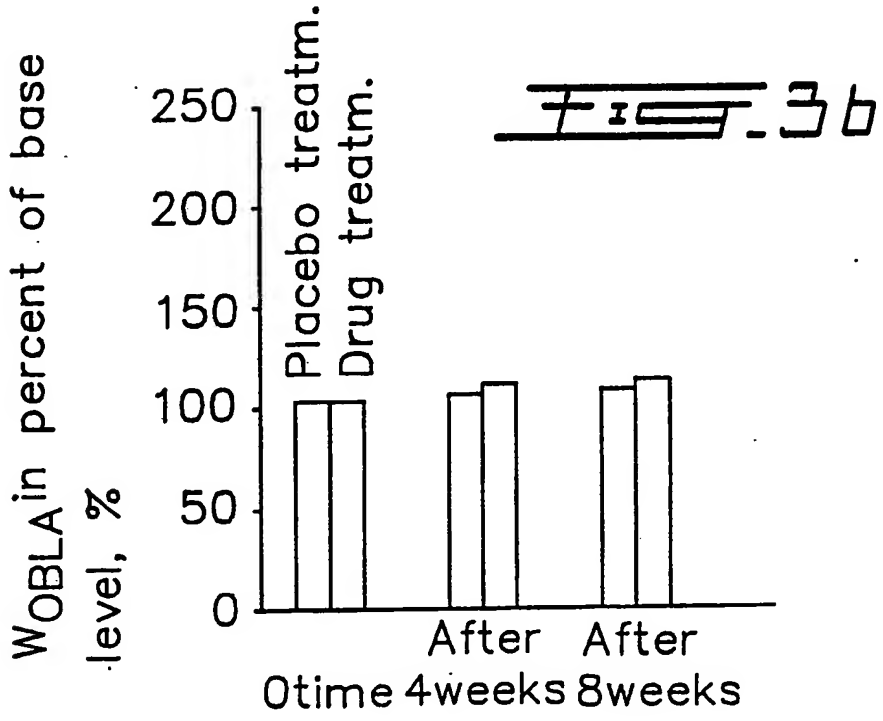

W_{OBLA} in percent of base level, %
250
200
150
100
50
0
Placebo treatm.
Drug treatm.
After
After
0time 4weeks 8weeks

FIG. 3C

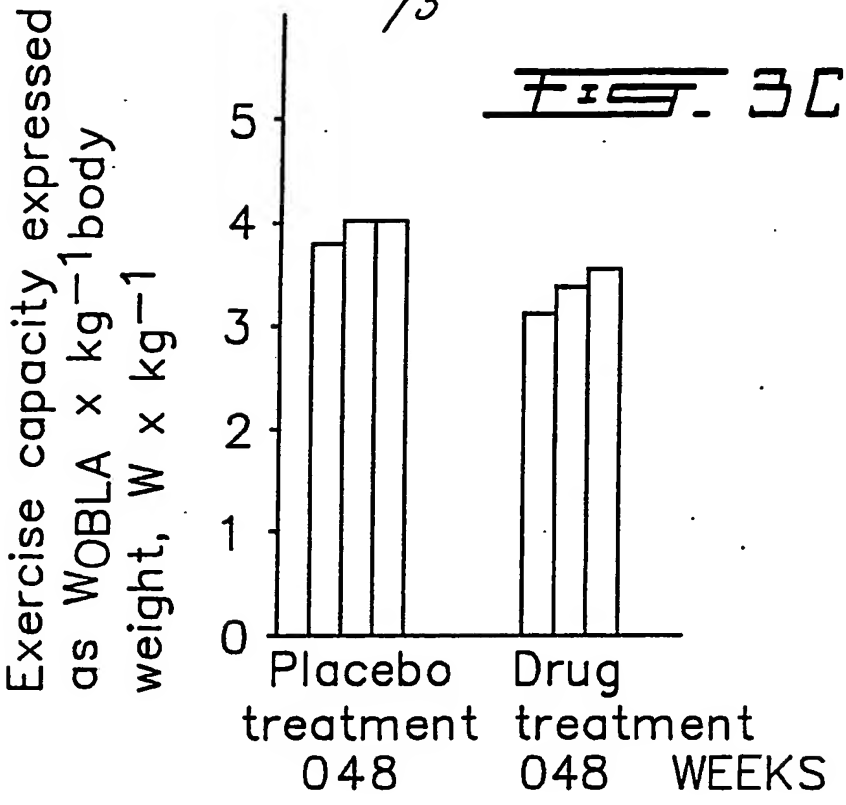
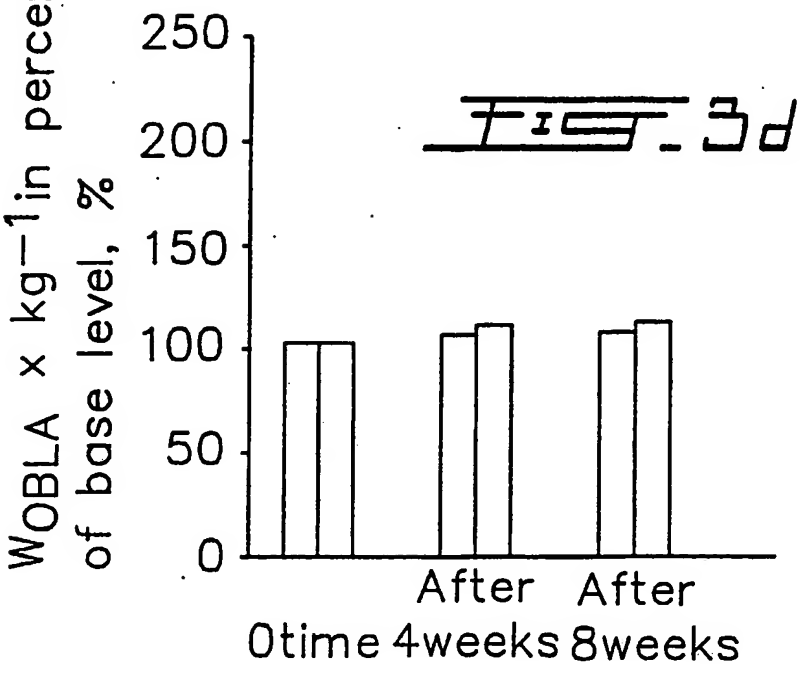

Exercise capacity expressed as $W_{OBLA} \times kg^{-1}$ body weight, $W \times kg^{-1}$
0
1
2
3
4
5
Placebo treatment
Drug treatment
0 4 8 0 4 8 WEEKS

FIG. 3d


$W_{OBLA} \times kg^{-1}$ in percent of base level, %
0
50
100
150
200
250
After
After
0time 4weeks 8weeks

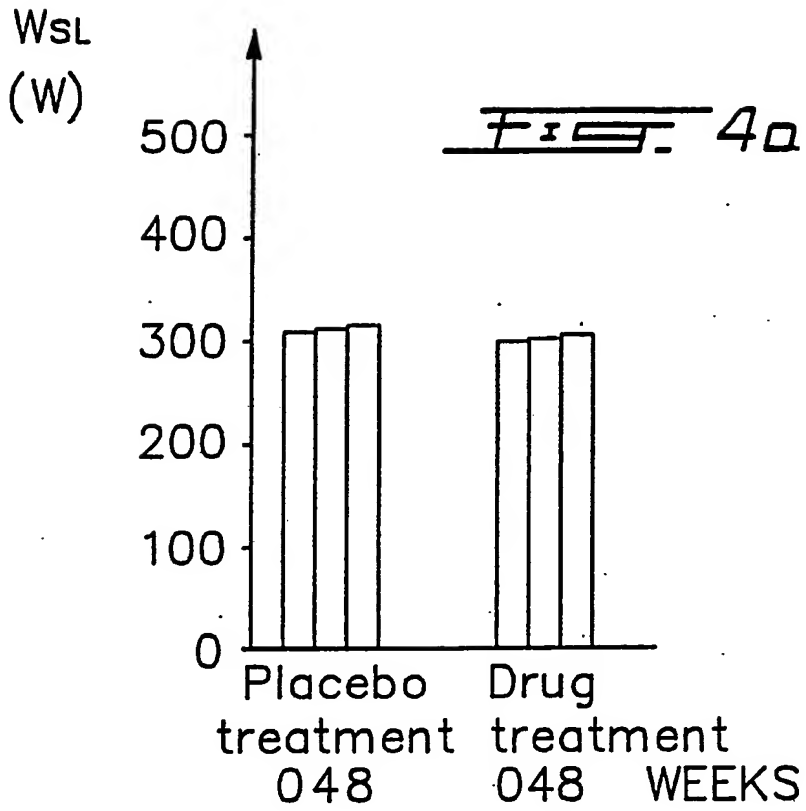

WSL
(W)
500
400
300
200
100
0
Placebo
treatment
048
Drug
treatment
048
WEEKS

Fig. 4a

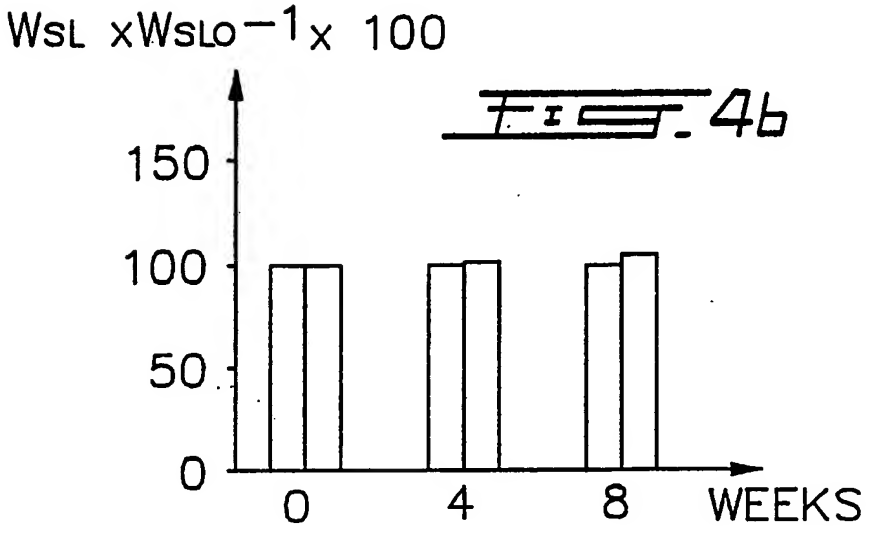

WSL xWSLO−1x 100
150
100
50
0
0
4
8
WEEKS

Fig. 4b

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE88/00436

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A 23 L 1/30, A 61 K 31/12

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC 4	A 23 L 1/29, 1/30; A 61 K 31/12, 37/48
IPC 1	A 61 k 19/00,/02, 27/00,/10 .../...

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

SE, NO, DK, FI classes as above.
CHEMABS, WPI(L), CLAIMS

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X Y	EP, A2, 0 100 459 (EISAI CO., LTD) 15 February 1984 see claims 1,2 and page 7, lines 11, 14-15 & JP, 59010511 CA, 1209908	1 1-14
X Y	Patent Abstract of Japan, Vol. 6, Nr.165, C 121 abstract of JP 57-79891, publ. 1982-05-19	1 1-14
X Y	Derwent's abstract No 87-146796/21, JP 62-083895	1 1-14
X	DE, A1, 3 405 581 (SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A.) 18 October 1984 see page 3, first paragraph & SE, 8400851 BE, 898918 GB, 2137088 FR, 2543827 .../...	1,2 1-14

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1988-10-24	1988 -11- 16
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Inga-Karin Petersson

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	JP, 59186914 NL, 8400488 CH, 655005 US, 4599232	
X	GB, A, 2 178 662 (SEUREF A.G.) 18 February 1987 see page 5, lines 18-35; claim 5 & BE, 905209 FR, 2585953 JP, 62059208 NL, 8601978 CH, 666184	1,3,7,9,10 1-14

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

II Fields searched (cont)

US Cl. 424:94,94.1; 426:442,531,544,648; 514:690

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 15,16 because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human body by therapy
PCT Rule 39 (iv)

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.